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Research Article

Application of Physicochemical Properties and Process Parameters in the Development of a Neural Network Model for Prediction of Tablet Characteristics

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Abstract. The importance of *in silico* modeling in the pharmaceutical industry is continuously increasing. The aim of the present study was the development of a neural network model for prediction of the postcompressional properties of scored tablets based on the application of existing data sets from our previous studies. Some important process parameters and physicochemical characteristics of the powder mixtures were used as training factors to achieve the best applicability in a wide range of possible compositions. The results demonstrated that, after some pre-processing of the factors, an appropriate prediction performance could be achieved. However, because of the poor extrapolation capacity, broadening of the training data range appears necessary.

KEY WORDS: artificial neural network; mechanical properties; plasticity; surface characteristics; tablet.

INTRODUCTION

The use of *in silico* modeling in the pharmaceutical industry is continuously increasing. This is due in part to the quality by design approach to new pharmaceutical product developments, which requires exact and well-supported design of experiments. However, the quality of pharmaceutical products has a multifactorial background that is influenced by many parameters. The screening of appropriate factors is time-consuming and demands considerable financial outgoings.

A decrease in the number of screening experiments through the use of artificial neural network (ANN) models for getting predictions based on previous data is of a great benefit (1). These systems demonstrate considerable advances over traditional factorial design of experiment (DoE) methods, including greater flexibility or their ability to handle a large number of input factors and to model nonlinear problems, which makes them a useful complementary method and/or extension of the DoE methods during the early pharmaceutical development by screening of the appropriate factors, and in the improvement of the production process via the processing and mining of data of the routine production (2). ANN models in basics mimic the structure and function of the human brain; they are adaptive, self-organizing and fault-tolerant. These principles make them able to accommodate to different problems, and hence ANNs are able to "learn". Thanks to these properties, ANNs demonstrate certain ability to predict the outcomes of a given data set. Their combination with other systems, such as neurofuzzy logic, leads to the added advantage of the generation of rule sets representing the cause–effect relationships contained in the experimental data (3). In recent years, there has been increasing interest in these systems with regard to formulation (4) or process optimization (5,6), often in association with a design space approach (2,7), as these examples from the field of solid dose forms supports. Systems of great interest are those in which the physicochemical properties of the raw materials are taken into account in the prediction of the product quality attributes (8–10). In these cases, however, considerable care must be taken concerning the selection of the appropriate inputs and learning parameters of the ANNs: an inappropriate (small, narrow range, etc.) training data set or the non-inclusion of important factors strongly limits the predictive capacity of the systems and restricts the possibility of predicting outcomes based on new data. We set out to develop a neural model that can be used in the early screening of suitable tablet formulations in a quality by design development, through prediction of the postcompressional properties of various scored tablet formulations. The assurance of the appropriate mechanical properties is a poorly studied field of pharmaceutical technology. Most of the articles are dealing with the question from clinical side through the problems of the application. The technological aspects were investigated in our previous studies (11–13), and the present work applies the data of these former results.

MATERIALS AND METHODS

Drotaverine hydrochloride, microcrystalline cellulose (Vivapur 102, J. Rettenmeier & Söhne, Germany), spray-dried mannitol (Pearlitol SD 200, Roquette Pharma, France),

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agglomerated α-lactose monohydrate (Tablettose 70, Meggle Pharma, Germany) and magnesium stearate (Ph. Eur.) were used to prepare samples. The compositions are presented in Table I.

The powders were mixed with a Turbula mixer (Willy A. Bachofen Maschienenfabrik, Switzerland; 8 min+2 min after the addition of the lubricant, at 50 rpm). The surface free energies of the materials and mixtures were determined with a Dataphysics OCA 20 optical contact angle tester (Dataphysics, UK), with use of the sessile drop method. The method is based on measurement of the equilibrium contact angle, the value of which is determined by the surface tensions in the solid, liquid and vapour phases, described by the Young equation (Eq. 1):

$$0 = \gamma_{SL} - \gamma_{SV} - \gamma_{LV}\cos\theta \quad (1)$$

where θ is the equilibrium contact angle, γ is the surface tension between the given phases, S is solid, L is liquid and V is vapour. The disperse and polar components of the solid materials were calculated with the Wu equations (Eqs. 2 and 3) in the knowledge of the surface tensions of polar (water) and apolar (diiodomethane) test liquids. The liquids were dropped onto the surface of comprimates 10 mm in diameter prepared with a Specac hydraulic press (Specac Inc, UK) at a pressure of 4 tons.

$$(1+\cos\ \theta)\gamma_1 = \left((\gamma_1^d\gamma_s^d)/(\gamma_1^d+\gamma_s^d)\right) + \left((\gamma_1^p\gamma_s^p)/(\gamma_1^p+\gamma_s^p)\right) \quad (2)$$

$$(1+\cos\ \theta)\gamma_2 = \left((\gamma_2^d\gamma_s^d)/(\gamma_2^d+\gamma_s^d)\right) + \left((\gamma_2^p\gamma_s^p)/(\gamma_2^p+\gamma_s^p)\right) \quad (3)$$

where γ^d is the disperse and γ^p is the polar component of the surface tension, γ_1 is the surface tension of the first and γ_2 is the surface tension of the second test liquid, and γ_s is the surface free energy of the solid material.

The polarity of materials can be calculated as the quotient of the polar and the total surface free energy (Eq. 4).

$$\text{Polarity(percentage)} = \gamma_s^p/\gamma_s \quad (4)$$

where y_s^p is the polar component of the surface free energy and γ_s is the total surface free energy of the solid material.

The strength of the adhesion between the different materials can be characterized by the value of the work of adhesion, which can be calculated via the following equation (Eq. 5):

$$W_a = \left((\gamma_1^d\gamma_2^d)/(\gamma_1^d+\gamma_2^d)\right) + \left((\gamma_1^p\gamma_2^p)/(\gamma_1^p+\gamma_2^p)\right) \quad (5)$$

where γ^d is the disperse and γ^p is the polar component of the surface free energy, γ_1 is the surface free energy of the first and γ_2 is the surface free energy of the second material.

The plasticities of materials and mixtures were determined with a computer-connected Korsch EK0 (E. Korsch Maschienenfabrik, Germany) eccentric tablet press, instrumented with strain gauges on both punches and a displacement transducer (Micropulse, BTL5-A11-M0050-P-532, Balluff, Germany) on the upper punch. The strain gauges were calibrated with a Wazau HM-HN-30kN-D cell (Kaliber Ltd., Hungary). The transducer distance accuracy was checked by using five measuring pieces of accurately known thickness (1.0, 2.0, 5.0, 7.5 and 10.0 mm) under zero load (Mitutoyo, Japan). The materials and mixtures were filled into the die and compressed manually (to ensure similar conditions for the well and poorly compressible materials) in the compression force range from 1 to 30 kN. The plasticity was calculated from the results of force displacement measurements with the Stamm–Mathis equation (Eq. 6):

$$Pl = E2/(E2+E3) \quad (6)$$

where *E2* and *E3* are the given areas of the force-displacement curve (14).

Samples S1–S8 were compressed on a Korsch EK0 eccentric- and on a Ronchi AM8S (Officine Meccanice F.lli Ronchi, Italy) rotary tablet press. For the compression of samples S9–S12, a Kilian SP300 (IMA, UK) eccentric press was used in a collaboration with University of Ljulbljana. All tablet presses were mounted with strain gauges, with flat single punches 8 mm in diameter, with a bisecting line. The air temperature was 22–25°C at a relative humidity of 57–65%. The tablet mass was 0.18 g, and the compression rate was 36 tablets/min. The applied compression pressure was 100, 200 or 300 MPa.

The hardness of the resulting tablets was measured with a Heberlein tablet hardness tester (Heberlein & Co. AG,

Table I. Compositions of Powder Mixtures

Sample	Vivapur 102 (g)	Pearlitol SD 200 (g)	Tablettose 70 (g)	Drotaverine HCl (g)	Magnesium stearate (g)
S1	50	50	–	–	1
S2	30	70	–	–	1
S3	10	90	–	–	1
S4	90	–	10	–	1
S5	70	–	30	–	1
S6	50	–	50	–	1
S7	30	–	70	–	1
S8	10	–	90	–	1
S9	85.5	9.5	–	5	1
S10	81	9	–	10	1
S11	76.5	8.5	–	15	1
S12	67.5	7.5	–	25	2

Table II. Physicochemical Properties of the Powder Mixtures

Sample	Surface free energy (mJ/m2)	Polarity (%)	Slope of plasticity funct.	Intercept of plasticity funct.
S1	70.95	40.04	−0.0864	90.821
S2	69.37	38.53	−0.0763	86.251
S3	68.60	38.67	−0.0688	85.385
S4	70.98	38.19	−0.0898	94.561
S5	70.47	38.73	−0.0740	89.688
S6	72.12	39.90	−0.0622	84.507
S7	72.09	40.50	−0.0520	80.321
S8	70.94	40.51	−0.0744	82.248
S9	78.04	41.66	−0.0591	95.010
S10	77.96	44.45	−0.0575	93.814
S11	76.95	42.68	−0.0642	93.933
S12	70.01	45.32	−0.0659	94.114

Table III. Compression Conditions and the Corresponding Tablet Properties

Sample	Tablet press	Compression pressure (MPa)	SD	Compression time (ms)	Tensile strength (MPa)	SD	Subdivision (%)
S1	Eccentric	136.40	27.50	320	1.61	0.24	60
		188.13	1.84	327	2.15	0.31	100
		259.64	2.15	344	2.35	0.17	80
	Rotary	84.40	1.87	139	0.73	0.27	10
		200.44	3.33	152	2.07	0.41	30
		302.47	2.27	162	2.65	0.36	40
S2	Eccentric	102.97	0.90	296	0.99	0.10	50
		186.31	1.49	330	1.61	0.18	80
		277.21	1.31	347	2.03	0.14	70
	Rotary	107.46	1.13	139	0.75	0.15	0
		192.05	3.37	153	1.77	0.14	10
		299.14	2.25	170	2.31	0.21	40
S3	Eccentric	120.96	1.44	317	0.85	0.11	30
		186.31	1.49	367	1.58	0.08	80
		300.17	1.16	363	1.83	0.23	90
	Rotary	107.80	2.29	134	0.46	0.06	0
		195.36	2.69	144	1.56	0.27	10
		305.38	3.34	153	2.46	0.45	30
S4	Eccentric	118.79	1.73	259	4.03	0.35	60
		202.13	3.65	291	5.91	0.52	70
		314.87	4.94	360	6.20	0.62	90
	Rotary	102.31	1.43	144	2.98	0.37	0
		204.03	3.15	158	5.43	0.28	20
		287.77	2.82	166	5.72	0.32	40
S5	Eccentric	121.42	1.93	280	3.46	0.14	50
		216.17	4.64	321	4.09	0.24	30
		310.83	2.22	348	4.44	0.30	30
	Rotary	96.96	0.86	149	2.06	0.18	0
		199.56	4.42	153	3.51	0.14	60
		302.57	2.92	164	3.90	0.40	70
S6	Eccentric	83.50	1.19	301	1.82	0.11	20
		225.96	1.73	341	3.21	0.35	20
		321.06	1.74	368	3.29	0.38	40
	Rotary	103.67	1.48	143	1.37	0.17	0
		193.24	3.06	152	3.11	0.34	0
		294.90	3.52	160	3.07	0.40	10
S7	Eccentric	112.06	0.79	291	1.30	0.19	10
		208.43	1.47	304	2.17	0.38	10
		303.19	2.41	326	2.71	0.44	50
	Rotary	102.35	1.62	135	0.66	0.12	0
		198.83	4.22	154	1.52	0.30	0
		290.68	7.72	153	2.21	0.38	0
S8	Eccentric	103.35	2.03	284	0.60	0.10	0
		208.59	2.68	306	1.12	0.17	0
		272.43	1.46	387	1.25	0.23	10
	Rotary	96.93	2.25	135	0.25	0.05	0
		217.60	9.17	146	1.05	0.22	0
		312.48	7.66	151	1.49	0.18	20
S9	Eccentric	106.60	1.50	263	2.08	0.17	50
		193.57	3.03	267	2.00	0.22	90
		292.85	5.52	299	1.74	0.29	90
S10	Eccentric	102.55	1.16	258	1.98	0.23	63
		198.37	3.29	267	1.97	0.14	100
		284.17	2.61	293	1.84	0.14	90
S11	Eccentric	120.83	2.52	258	2.85	1.19	70
		202.50	4.05	270	2.74	0.15	70
		284.13	2.28	275	2.45	0.17	100
S12	Eccentric	109.16	1.46	254	1.74	0.10	40
		198.73	4.14	260	1.92	0.11	72
		281.48	6.55	270	1.79	0.11	70

Switzerland). To the better comparison of the hardness of tablets with different geometrical parameters, the tensile strength of tablets was calculated according to the Fell-Newton equation (Eq. 7) (15,16).

$$\sigma = 2F/\pi Dt$$

Where F is the applied force, D is the tablet diameter and t is the thickness of the tablet.

For measurement of the force required to break the tablets into halves, and get information about the ratio of the appropriate subdivision of tablets, a laboratory-constructed hardness tester was utilized, with three-bend tablet hardness testing. The tablet must be centered under the breaking item, which moves vertically down. The load is detected with a computer-connected measuring cell, which is placed under the sample holder table (11).

The results were analysed with the Neural Network module of the StatSoft Statistica 6.1 software (StatSoft Inc., Tulsa, Oklahoma, USA). Twelve formulations were compressed into tablets, eight of them (S1–S8) in both eccentric and rotary presses (11). Three different compression pressures were applied in every case. The data on 20 tablets were collected in each of 60 settings. The results on samples S7, S9 and S10 (0, 1 or all of the physicochemical parameters, respectively, lay outside the training set (see below), demanding more or less data extrapolation during the modeling) and some randomly selected cases from the other settings were used for external validation of the prediction performance. The data on randomly selected 490 tablets were used for training, randomly divided into training, selection and test sets, containing 400, 45 and 45 cases, respectively. The selection set was dedicated to the internal validation of the prediction performance during the training, while the test set was utilized for internal validation after the training. The internal validation was performed according to a tenfold cross-validation scheme. As external validation, the correlation between the observed and predicted values of the selected data sets was tested.

The prediction performances of the different models were compared with the non-parametric Kruskal–Wallis test, with the use of *post hoc* comparisons. Use of the non-parametric test was necessary because of the small number and unknown distribution of the studied samples. The statistical analysis was carried out with the StatSoft Statistica 8 software.

RESULTS

The aim of the current study was to investigate how the results and findings of previous studies (12,13) can be implemented into the development of an ANN for general modeling of similar processes. As mentioned above, one of the most important problems in neural modeling is the selection of appropriate training factors among the numerous physicochemical properties of the materials and process parameters of the compression influencing the final tablet characteristics. The main conclusions of the above mentioned studies were that for characterization of the physicochemical properties of the applied materials, the surface free energy, polarity index (good descriptors and predictors of inter-particulate interactions) and deformation properties seem to be appropriate parameters. The commonly used indices, such as the Heckel, Walker and Kawakita, are poorly applicable due to their constant nature. No direct relation can be drawn with the actual process parameters. The problem necessitates the use of parameters which can describe the actual behavior of the system. The shape parameters of the Stamm–Mathis plasticity-compression force function should be appropriate indices. The parameters applied for the training of the models are displayed in Table II.

Concerning the process parameters, besides the applied compression force (the most important process parameter), the tablet compression time and the mechanism of compression (determined by the type of tablet press) are also important. The conditions of compression with the corresponding tablet properties are presented in Table III.

DISCUSSION

Surface free energy, polarity index, shape parameters of the plasticity function, compression force and compression time were used as input variables; the output variables were the tensile strength and the breakability (subdivision or halving properties) of the tablets. On the basis of previous results (13), an MLP network was used with $n+m+1$ hidden neurons (Fig. 1a).

Delta-bar-Delta (17) was used as the training algorithm. The minimum error level was reached in less than 100 training epochs. The results of the internal validation revealed an excellent correlation between the observed and predicted data (R^2=0.924). However, the predictive force of the network in external validation tests was very poor (R^2<0.1). The system made no differentiation between tablets prepared at different

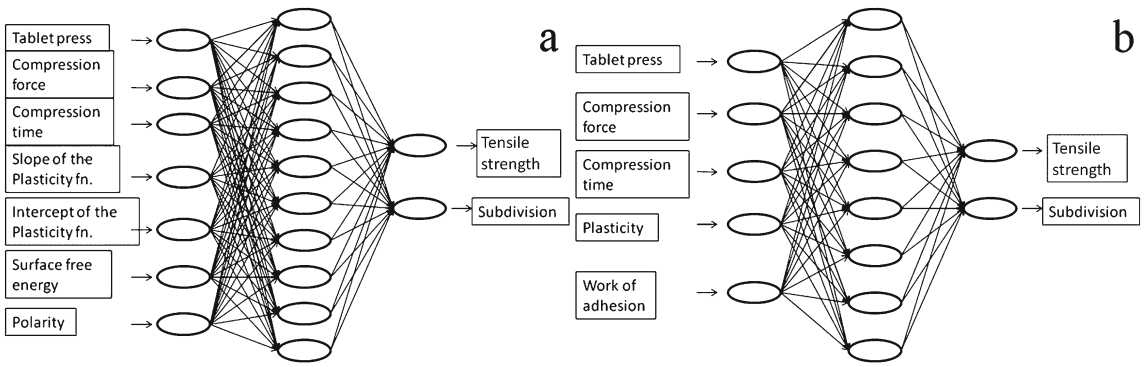

Fig. 1. The structure of the network before **a** and after **b** the modification of the data preprocessing

compression forces; only the difference between samples was visible. The results did not improve either in response to the change to different backpropagation- or gradient-based training algorithms or to the changes in the complexity of the system via the modification of the number of hidden neurons or layers. This is probably due to the high proportion of the material-related parameters among the input variables, which made it necessary to reduce these parameters in the original data set. The pruning of input factors was impossible during the network training, the omission of information from the model resulting in a decrease in prediction performance. As the application of less information in such a complex model should be avoided, combination of the different parameters with computational preprocessing (18) appeared to be more advantageous. The surface free energies and polarity indices of the materials were replaced by the calculated work of adhesion against stainless steel, and the shape parameters of the plasticity function were replaced by the calculated plasticity value corresponding to the applied compression force. The modified structure is displayed in Fig. 1b.

The preprocessing of the training data was effective because the training with the modified data set was followed by a significant increase in the prediction performance of the system ($p<0.05$). However, both the Delta-bar-Delta and the quick-propagation algorithm converged too quickly with the previously applied stopping conditions. The changes in the stopping conditions, e.g. in the minimum improvement in the selection set from 0.001 to 0.01 and the window from 10 to 100 epochs, resulted in some, but not significant improvement. Further improvement was achieved when the training algorithm was changed to back-propagation, which in this case provided greater accuracy at the expense of slower convergence. For the best model, a second training phase was used, with a gradient-based quasi-Newton algorithm (19).

The results of the internal testing demonstrated appropriate observed *vs.* predicted correlation coefficients (R^2=0.874 for the tensile strength and R^2=0.899 for the breakability). However, the external testing of the prediction performance yielded much poorer results. There was no correlation between the observed and the predicted tensile strength (Fig. 2), and the data seemed to be slightly overestimated.

Nevertheless, when only those data which were within the limits of the training data set and required no extrapolation were investigated, the correlation coefficients increased significantly (R^2=0.7823). The reason for this may be that, when some parameters were outside the training set, and therefore an extrapolation calculation was necessary in the modeling, the overestimation of the data was considerably higher and the results displayed a negative correlation. Moreover, it is clearly visible that because of the stopping conditions of the learning mechanism, the natural deviation of the tensile strength (caused by the slightly different compaction conditions) cannot be followed by the smoothing of the response surface. However, the increase of the model sensitivity resulted in an overfitting of the model. Nevertheless, if the disturbing effect of the hardness deviation is taken into account, and the results are compared with the average hardness of the different compositions, the values of the correlation can be further improved (Fig. 3).

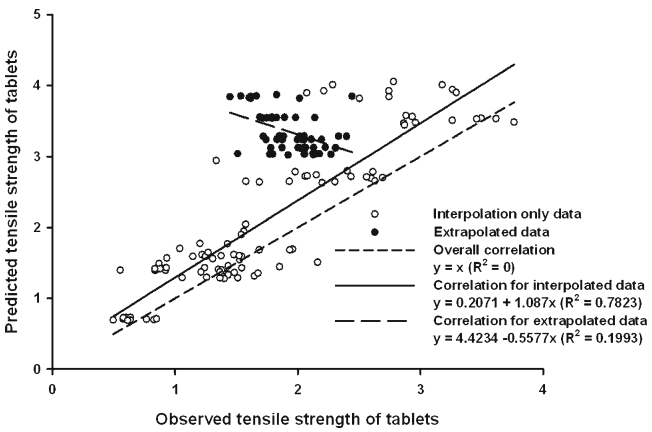

Fig. 2. Correlations of observed and predicted tensile strength

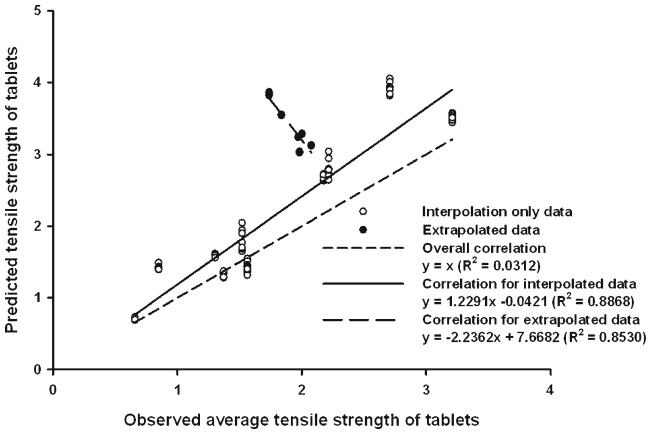

Fig. 3. Correlations of observed and predicted average tensile strength

For the breakability, the external testing also gave poorer results than the internal testing. The halving properties were usually overestimated for lower values, and slightly underestimated for higher ones (Fig. 4). However, when these deformations are taken into account, appropriate screening can be carried out for the potentially well-breakable compositions, despite the poorer correlations.

CONCLUSIONS

An ANN model was developed on the basis of existing data for prediction of the postcompressional properties of tablets prepared from independent samples. The main benefit

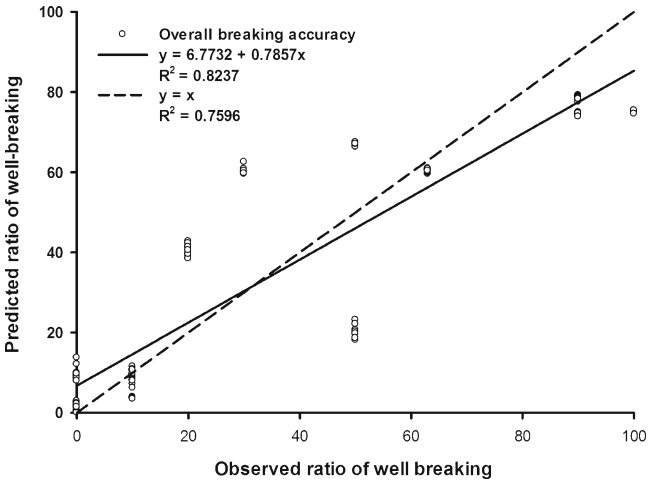

Fig. 4. Correlations of observed and predicted breakability

was that the tablet properties could be predicted applying appropriate physicochemical properties of mixtures, irrespectively of the composition. In the present work, the applied data originated from three different experiments, including both API free and API containing compositions. The main limitation is that, despite of the theoretical possibility, the model has a poor extrapolation capacity, which can be solved with the implementation of data into the model, which are out of the range of the original data set. However, the extension of the ranges requires a large number of further experiments if there is no possibility to collect data from the results of other existing experiments. The incrementing of the training data could be advantageous also from the aspect of the decreasing of the effect of the unpredictable inter-individual deviation of the tablet properties.

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